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Medical Progress

Antimicrobial Agent-Associated Colitis and Diarrhea

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Although antimicrobial agent-associated colitis has been recognized as a clinicopathologic entity for years, the cause of this disease has been determined only recently. Virtually all cases of pseudomembranous colitis and some cases of antimicrobial agent-associated nonspecific colitis or diarrhea have been shown to be caused by a toxin of Clostridium difficile. *Methods for cultivating* C difficile *from feces and for detecting the toxin have been developed. Oral administration of vancomycin has proved to be effective for the treatment of* C difficile*-induced colitis, although isolated instances of relapse after treatment have been documented.*

The discovery of C difficile *as a human intestinal pathogen has provided an explanation for some, but not all cases of antimicrobial agent-associated diarrhea. The epidemiology, pathogenesis and means of prevention of* C difficile *toxin-induced diarrhea remain to be determined.*

ALTHOUGH GASTROINTESTINAL SIDE EFFECTS are probably the most common adverse effects of antimicrobial therapy, the cause of the most serious of these, pseudomembranous colitis, has only recently been elucidated. Bartlett and coworkers[1] and Rifkin and colleagues[2] discovered that a toxin produced by *Clostridium difficile* was the cause of ileocecitis in hamsters given clindamycin. Techniques developed during study of this hamster model have been applied to antimicrobial agent-associated diarrhea in humans, with impressive results. *C difficile* toxin has been shown to be the cause of virtually all cases of pseudomembranous colitis.[3-7] In addition, some cases of antimicrobial agent-associated diarrhea (in which a pseudomembrane is not present) appear to be caused by this toxin.[3,6] These diseases are unique in that an organism which may normally be found in the human colon, causes illness only after administration of antimicrobial agents.

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Terminology

A great deal of confusion surrounds pseudomembranous and antimicrobial-associated diseases

of the gut. Pseudomembranous *entero*colitis is an entity, first described in the preantibiotic era,[8] in which a gastrointestinal operation or hypotension was a common if not essential substratum. Diarrhea occurred in less than half of the patients, involvement of the gastrointestinal tract was usually most prominent in the small bowel and death was common.[9] During the 1950's and 1960's, the same or a similar disease was attributed to overgrowth in the bowel of enterotoxin-producing *Staphylococcus aureus,* presumably as a sequela of antimicrobial therapy. Formation of gastrointestinal pseudomembrane has also been attributed to leukemia, heavy metal intoxication, bowel obstruction, cardiac disease and uremia.[9] Gorbach and Bartlett question whether either *S aureus* or antimicrobial therapy should be considered as possible causes of pseudomembranous *entero*colitis.[9] Retrospective analysis of such cases is fraught with problems because of variable and often inadequate criteria for diagnosis. Antimicrobial agent-associated (pseudomembranous) colitis does not involve the small bowel, and should be considered as an entity distinct from pseudomembranous *entero*colitis and staphylococcal colitis.

Results of sigmoidoscopy in combination with rectal biopsy have been used to categorize antimicrobial agent-associated diarrhea as pseudomembranous colitis, nonspecific colitis and diarrhea without colitis.[10-12] Several problems are inherent in this type of classification. Sumner and Tedesco[12] have documented the progression of nonspecific antimicrobial-associated colitis to pseudomembranous colitis. It is likely that in such patients diarrhea developed first, then nonspecific colitis and, finally, pseudomembranous colitis.

Volpicelli and co-workers[13] and others[14,15] have described sparing of the rectosigmoid colon in patients with antimicrobial agent-associated colitis of the right side. Unfortunately, neither *C difficile* nor its toxin was sought in any of these cases. Tedesco[16] has recently reported five cases of patients with toxin-positive pseudomembranous colitis as documented by colonoscopy; in each instance results of sigmoidoscopy were negative. Thus, the limitations of a disease classification based on sigmoidoscopic findings are evident—gross and microscopic pathological findings may change significantly over several days, and may also vary from segment to segment of the colon. Because therapeutic considerations are based on the presence of toxin in feces as well as pseudomembrane or plaque formation, *Clostridium difficile*-induced colitis (or diarrhea) may be a more appropriate term.

Clostridium difficile-Induced Ileocecitis in Hamsters

Small,[17] in 1968, described the consistent development of a fatal ileocecitis in Syrian hamsters after administration of lincomycin. Green[18] noted that material taken from hamsters or guinea pigs dying of penicillin-induced ileocecitis produced a cytopathic effect in WI-38 cells, and concluded that a latent virus was responsible. Other investigators later found that a single dose of clindamycin (as well as a variety of other antimicrobial agents) would also cause ileocecitis[19-22]; disease was either prevented or postponed when vancomycin was given orally around the time of the clindamycin challenge.[23,24] A transmissible agent was implicated when Bartlett and colleagues[1] found that serial passage of cecal contents from diseased to healthy untreated hamsters consistently caused ileocecitis in the recipient; assay of cecal contents for clindamycin was negative after the first two or three passages. When the cecal contents from a hamster dying of ileocecitis were filtered (to remove bacteria and viruses) and then injected intracecally into a healthy animal, ileocecitis still developed in the recipient.[1] However, if the cecal contents were heated[25] or incubated with polyvalent gas gangrene antitoxin before injection,[1] ileocecitis did not develop in the recipient. Thus, hamster ileocecitis was found to be a disease that could be prevented by vancomycin administration and that was caused by a transmissible agent.

The filtration studies and the finding that ileocecitis could be prevented by heating or incubating cecal contents with gas gangrene antitoxin suggested that a toxin, probably of clostridial origin, was involved. Subsequent studies showed that this toxin was produced by *Clostridium difficile.*[1,3,26] This elegant series of experiments satisfied Koch's postulates for disease due to a transmissible agent. A less cumbersome and more rapid means of toxin detection was developed when it was noted that *C difficile* toxin produces a cytopathic effect in tissue culture.[3,25-31] This cytopathic effect is probably the same as that detected by Green in hamsters and guinea pigs dying of penicillin-induced ileocecitis.[18] Detection of *C difficile* toxin in feces by cell culture assay has been used

extensively to study antimicrobial-associated diarrhea in humans.[3-7,10,16,26]

Sources of *Clostridium difficile*

C difficile has been isolated from a variety of sources. The organism was first described and named *Bacillus difficilis* in 1935 by Hall and O'Toole, who recovered it from the feces of four of ten healthy newborn infants.[32] In 1940 Snyder reported the isolation of *B difficilis* from the feces of 10 of 22 healthy infants during the first year of life.[33] Several other studies have confirmed the presence of *C difficile* in the feces of asymptomatic infants.[34-36]

In contrast, *C difficile* was isolated from the feces of only 4 of 137 patients undergoing detailed fecal flora studies.[37] The low incidence of carriage in this study may have been due to the extremely complex fecal flora of adults and to the lack of a highly selective medium for *C difficile* at the time the study was done.

C difficile was also isolated from the urogenital tract of 100 percent of men suffering nonspecific urethritis and from 72 percent of women attending a venereal disease clinic.[38] This latter finding suggests that newborn infants may become colonized during passage through the birth canal.

C *difficile* has been isolated on rare occasions from blood,[39,40] pleural fluid,[39] peritoneal fluid[39] and soft tissue infection (usually related to surgical operations of the bowel).[29,30,40] Smith and King[39] were unable to attribute definite pathological significance to the recovery of *C difficile* in such instances.

Reports of isolation of *C difficile* from the environment are limited. Hafiz and Oakley[34] recovered the organism from sand, soil and mud (as well as from donkey, horse and camel dung). The only hospital environmental isolation of *C difficile* was reported by Keighley and co-workers,[41] who recovered it once from a shelf on which bedpans were stored. In the latter instance, "repeated searches in the ward environment" were made because of continual occurrence of *C difficile* colitis on a surgical ward. Contamination of the hospital environment could explain the reported clustering of cases of colitis.[6,42] The isolation of *C difficile* from soil and feces of domesticated animals suggests that contamination of food (vegetables by soil and animal carcasses by feces during slaughter) is another potential source for infection of the human gut.

Pathogenesis

Agents reported to have caused pseudomembranous colitis are invariably present in feces, often in a very high concentration.[43] These agents may alter the normal gut flora so as to render it incapable of suppressing growth or toxin elaboration by *C difficile*. The mechanism by which the normal flora might prevent the proliferation of *C difficile* is not known; however, competition for mucosal attachment sites, production of chemical inhibitors, or use of nutrients essential for growth of *C difficile* have been postulated.[29,37] Once *C difficile* becomes established in the gut of a "susceptible" patient it may proliferate to achieve high counts and elaborate quantities of toxin sufficient to cause colonic mucosal injury. Reports of colitis developing up to three weeks after the inciting antimicrobial agent has been discontinued suggest that the intestinal microflora may not be reconstituted for some time.[44] Diarrhea has not developed in all adult patients with high fecal counts of *C difficile*[29,45] (an observation also made by W. L. George, M. E. Mulligan and S. M. Finegold, unpublished data, 1979) nor has it occurred in all infants or adults with *C difficile* and toxin in their feces.[36,45,46] Therefore, other factors such as host susceptibility to the effects of toxin must be important.

Clostridium difficile Toxin

The toxin of *C difficile* has been purified and partially characterized by several different groups of investigators who have reported molecular weights of approximately 107,000, 240,000 and 550,000 daltons.[28,47-50] Treatment of the 550,000 dalton moiety with strong reducing agents yields 50,000 dalton polypeptide chains; thus, the various molecular weights reported may represent differences in methods used for toxin purification. Inactivation of the toxin by amylase and proteolytic enzymes indicate that the toxin is a glycoprotein.[47] The toxin is present in the cytoplasm of the organism and is released upon bacterial cell lysis.[47] Controversy exists as to whether all strains of *C difficile* elaborate toxin[26,30,51]; apparent discrepancies in toxigenicity may simply reflect the various broth media employed and the varying nutritional requirements of different strains of *C difficile*. This latter possibility may be of relevance, however, because certain essential nutrients might be lacking in the human gut. It is clear, in

any case, that the vast majority of strains produce toxin. There is, however, considerable variability in the amount of toxin each produces.

The mechanism of action of the toxin is not known. Studies to date indicate that it causes a cytopathic effect in a variety of cell culture lines,[3,27,28,46-53] ileocecitis in hamsters,[10] and fluid accumulation in the isolated rabbit ileal loop assay[28] (but not in the suckling mouse assay[25]); it also increases vascular permeability in the rabbit dermis[47] and stimulates colonic guanylate cyclase in vitro.[52] Chang and co-workers[54] have recently shown that the toxin binds to the lipid portion of intracellular membranes. Adenyl cyclase, Na^+-K^+-ATPase and steroidogenesis in cell culture are not affected.[27,52]

In earlier studies, the cytopathic effect of feces from patients with colitis, and from hamsters with ileocecitis was found to be neutralized by the component of polyvalent gas gangrene antitoxin directed against *Clostridium sordellii* toxin. This finding initially led to suggestions that *C sordellii* was the cause of colitis.[5,55] Chang and co-workers[56] and others, however, have convincingly shown that neutralization of toxicity is an immunological cross-reaction between *C difficile* toxin and *C sordellii* antitoxin. *C sordellii* has not been shown to have any role in the development of colitis in humans or ileocecitis in hamsters.

Wilkins[52] has developed an antibody to the toxin of *C difficile*. If this antitoxin proves to be specific, then a simple immunological means for detecting toxin, such as gel diffusion, should be possible.

Pathology

Visualization of the colonic mucosa by sigmoidoscopy or colonoscopy may show adherent whitish-green or yellow, raised mucosal plaques[57,58]; the plaques may occasionally coalesce to form an extensive pseudomembrane. The intervening mucosa is typically erythematous, edematous and, occasionally, friable.[57,58] On microscopic examination, the well-formed pseudomembrane is seen to consist of mucin, fibrin, polymorphonuclear leukocytes and sloughed epithelial cells.[11,12,57] Microscopy of a rectal biopsy specimen in both pseudomembranous and nonspecific colitis will show infiltration of the lamina propria and, sometimes, submucosa, by acute or chronic inflammatory cells, or both, as well as focal necrosis of colonic epithelium (Figure 1). Dilatation of mucus-secreting glands is sometimes present, whereas crypt abscess, vasculitis and vascular thrombosis have not been noted.[11,12]

Involvement of the colon may be patchy, with sparing of the rectosigmoid segment.[13-16] Hence, previously reported cases of *C difficile*-induced diarrhea and nonspecific colitis may actually have been pseudomembranous colitis with rectal sparing.

Inciting Agents

Agents which have been reported to cause pseudomembranous colitis are shown in Table 1. Although lincomycin, clindamycin and ampicillin have been the most commonly reported causes of colitis, several recent reports have implicated various cephalosporins.[7,16,62-64] *C difficile* and its toxin have also been detected in the feces of one patient with diarrhea and another with nonspecific colitis in association with cefoxitin administration (L. George, M. Mulligan, and S. M. Finegold, unpublished data, 1979).

Antituberculous agents, urinary antiseptics (methenamine mandelate, nalidixic acid and nitro-

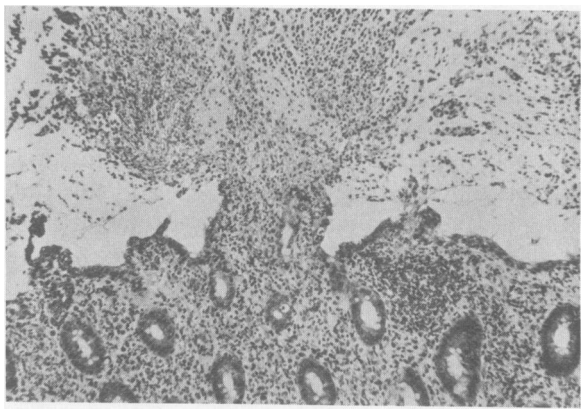

Figure 1.—Rectal biopsy specimen showing a plaque (superiorly) that is attached by stalk to the mucosa; inflammatory cell infiltrates are present in the lamina propria mucosae. (Reprinted by permission from Sumner & Tedesco[12]; copyright 1975, American Medical Association.)

TABLE 1.—*Agents Implicated as Causes of Colitis*

Penicillin[5,13-15,60]	Cefazolin[7,64]
Ampicillin[13,14,16,60,61]	Cefoxitin (see text)
Amoxicillin[13,14]	Tetracycline[60,61,66]
Nafcillin[7]	Chloramphenicol[7,66]
Lincomycin[61]	Metronidazole[61]
Clindamycin[44,60]	Cotrimoxazole[61,67]
Cephalexin[7,16,62,63]	Spiramycin[68]
Cephalothin[7,10,64]	Erythromycin[7]
	Aminoglycosides (orally given)[7,61]

furantoin) and aminoglycosides administered parenterally have not been implicated as causes of colitis.

Clinical Presentation

Diarrhea may develop at any time during, or up to three weeks following cessation of antimicrobial therapy; in occasional instances the onset of diarrhea may be as early as the second or third day of therapy.[44]

Typical symptoms and signs are watery diarrhea, nausea, vomiting, abdominal pain or cramps, low grade fever and leukocytosis.[44] In more severe cases, intense abdominal pain, high fever and pronounced leukocytosis may simulate acute intra-abdominal processes such as ruptured viscus, appendicitis or diverticulitis.[44] Protein-losing enteropathy, toxic megacolon, colonic perforation and shock are infrequent complications of antimicrobial agent-associated colitis.[44,69-73] Several deaths have been reported.

Bloody diarrhea may develop, particularly in association with penicillin or ampicillin therapy.

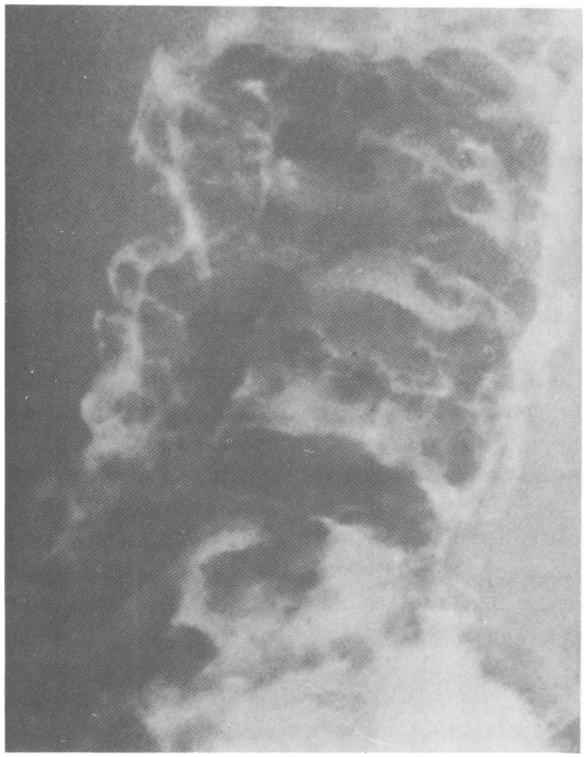

Figure 2.—Enlarged picture from an air-contrast barium enema study in a patient with pseudomembranous colitis; discrete, plaque-like lesions of the mucosa are evident. (Reprinted from Tedesco et al,[58] by permission from the *New England Journal of Medicine* 290:842, 1974.)

In such cases patients may have extensive mucosal erosions and inflammation of the proximal colon with relative or complete sparing of the rectosigmoid colon.[13-15]

Diagnosis

Definitive diagnosis in patients with antimicrobial agent-associated colitis requires the determination of extent and type of colonic pathological features, as well as of the causative agent and its toxin. *C difficile* colitis rarely, if ever, develops in the absence of antimicrobial therapy; therefore, a history of concurrent or recent antimicrobial therapy is essential. Gastrointestinal infection with *Campylobacter, Salmonella, Shigella, Yersinia* or *Entamoeba histolytica* may coincide with antimicrobial therapy and should be excluded by appropriate culture and microscopic examination. Pseudomembranous *entero*colitis must always be considered if the clinical features are consistent with that diagnosis. Gram-positive bacilli with subterminal spores and leukocytes may be present in the feces of patients with *C difficile* colitis or diarrhea, and these can be shown by Gram stain.

Most reported cases of pseudomembranous colitis have been documented by sigmoidoscopy. The recent reports of pseudomembranous disease of the proximal colon, with sparing of the rectosigmoid, indicate that negative results of a sigmoidoscopic examination do not exclude this diagnosis. In such cases a barium enema examination or colonoscopy should be done unless contraindicated. Although radiographic findings on barium enema have often been said to be nonspecific, Tedesco and colleagues[58] have suggested that a very specific pattern of plaque-like mucosal lesions may be detected, particularly if an air-contrast barium enema study is done (Figure 2). Acute onset of ulcerative colitis usually can be excluded by findings on barium enema and sigmoidoscopy, or colonoscopy with biopsy.

C difficile can be detected by use of a recently developed selective medium[59] in the feces of virtually all patients with pseudomembranous colitis, and in the feces of some patients with either antimicrobial agent-associated nonspecific colitis or diarrhea without colitis. However, *C difficile* has also been recovered frequently from the feces of healthy infants,[32-36] occasionally from feces of asymptomatic adults[37] and from the feces of a high percentage of asymptomatic adults who have received cefoxitin[45] (also noted by W. L. George, M. E. Mulligan and S. M. Finegold, unpublished

TABLE 2.—*Likelihood That* Clostridium difficile *Is Cause of Diarrhea*

	Pseudomembrane Detected and Restricted to Colon	*Nonspecific Colitis or Diarrhea Without Colitis*
Toxin test and culture for *C difficile* not done	Probable	Possible
Culture positive for *C difficile*	Extremely likely	Possible
Toxin test results and culture positive	Diagnostic	Likely

data, 1979). Hence, the recovery of this organism from feces is suggestive of but not diagnostic for *C difficile*-induced diarrhea.

The finding of a cytopathic effect produced by fecal filtrates in tissue culture, and neutralization of that effect by *C sordellii* antitoxin, is an appreciably more specific test and, as such, carries definite therapeutic implications.[5-7,60] However, the limited instances of this toxin in the feces of asymptomatic adults receiving antimicrobial therapy and of infants who do not have diarrhea should always be kept in mind.[36,45,46] When toxin is detected in the feces of a patient with either antimicrobial agent-associated nonspecific colitis, or diarrhea without colitis, it is likely, though not absolutely certain, that *C difficile* (toxin) is the cause of diarrhea. When both colonic pseudomembranes and toxin are detected, the diagnosis is definitely *C difficile* colitis[3-6,16,36,55,60] (Table 2).

The cause of toxin-negative nonspecific colitis or diarrhea has not been determined and certainly warrants investigation.

Therapy

The most important aspect of therapy for antimicrobial agent-associated colitis or diarrhea is discontinuation of the offending drug.[7,44] Symptoms and colonic pathological features in documented cases of pseudomembranous colitis will usually resolve within one to two weeks of discontinuation of therapy.[44] Ridding the gastrointestinal tract of the source of toxin, *C difficile,* is important in cases that do not improve after discontinuation of the offending drug. Vancomycin is highly effective against all strains of *C difficile* tested; when given orally in a dosage of 125 to 500 mg four times per day for seven to ten days, it produces rather prompt resolution of symptoms and disappearance of *C difficile* and toxin from the feces.[3,6,7,60] When vancomycin is given in a total daily dose of 500 mg, fecal levels average 351 ± 172 mg per gram.[6] Such values are at least 200-fold higher than the minimal inhibitory concentration of vancomycin for *C difficile*.[7,43]

Keighley and colleagues[6] have carried out a randomized double-blind study of the response of diarrhea in postoperative patients to vancomycin or placebo. In eight of nine patients with fecal toxin present, improvement or resolution of diarrhea occurred within five days of treatment with 125 mg of vancomycin four times per day. In only two of seven patients with fecal toxin in the placebo-treated group did improvement occur. When patients with diarrhea, but not toxin, were treated with placebo or vancomycin, the latter agent was not found to be efficacious. Data are insufficient to establish adequate guidelines for therapy for all cases of *C difficile* toxin-induced diarrhea. Certainly, when symptoms are protracted, or when a patient is very ill, vancomycin should be administered orally. Mildly symptomatic patients might be managed by discontinuation of the offending agent and administration of cholestyramine. If symptoms do not improve in several days, then cholestyramine should be discontinued and vancomycin, 125 mg four times per day, should be given. Fekety[7] has noted that the total cost of vancomycin is $175 to $280 when given in a dosage of two grams per day for seven days.

Although ototoxicity and nephrotoxicity may occur with parenteral administration of vancomycin, such toxicity has not been reported in association with oral therapy. Although vancomycin is normally poorly absorbed from the gastrointestinal tract, low levels have been detected in the sera of a few patients receiving treatment for colitis.[7,65] Because vancomycin is excreted by the kidney, renal function and, possibly, serum levels of the drug should be monitored if underlying renal dysfunction is present.

In a study published in 1979[74] relapse of *C difficile* toxin-induced colitis occurred in three patients. Neither the mechanism of relapse nor the frequency of relapse could be determined in these cases. Relapse in one patient responded to retreatment with vancomycin, and in another to cholestyramine therapy. The third patient's relapse responded to vancomycin retreatment, but a second and fatal relapse ensued after vancomycin was discontinued.

Metronidazole is also extremely active against *C difficile,* but the low levels achieved in the gut have been thought to limit its use for treatment of colitis. However, successful therapy of colitis

or diarrhea in six patients has recently been reported.[75-77] The rare cases of pseudomembranous colitis attributed to metronidazole therapy indicate that caution should be exercised regarding its use for therapy of colitis.

Cholestyramine has been shown to bind the toxin of *C difficile*[78,79] and, in theory, might be expected to be efficacious. Kreutzer and Milligan[80] reported response to cholestyramine in 12 patients with pseudomembranous colitis. The mean time to resolution of diarrhea was 2.1 days after beginning treatment with this drug. However, cholestyramine was given to four of the 12 patients within one to two days of onset of diarrhea; because antimicrobial agent-associated colitis is often self-limited, these four patients might have responded to discontinuation of the inciting antimicrobial agent without the addition of cholestyramine. Limited data presented at a workshop on clindamycin colitis indicated that there was response in 50 percent of patients treated with cholestyramine.[81] Cholestyramine will also bind vancomycin[79]; it would seem appropriate to avoid the simultaneous use of the two agents whenever possible.

Constipating agents, such as diphenoxylate hydrochloride (Lomotil) and opiate derivatives, have also been suggested as therapy for antimicrobial agent-associated colitis or diarrhea.[82] Some investigators have noted that the use of such agents appears to prolong, rather than ameliorate, symptoms and have suggested that they may predispose to toxic megacolon.[81,83,84] Data that document the efficacy of corticosteroid therapy are even more limited and there is certainly a theoretical hazard.

Vancomycin appears to be the agent of choice at this time for therapy of colitis or diarrhea due to *C difficile* toxin. Metronidazole, cholestyramine and, possibly, orally given bacitracin or other agents, as well as immunotherapy and inactivation of toxin by heavy metals,[47] may also prove to be of value. The variable and often self-limited course of *C difficile* toxin-induced diarrhea requires that therapeutic efficacy by evaluated in a controlled fashion.

Conclusion

The cause of pseudomembranous colitis and some other forms of antimicrobial agent-associated diarrhea has been established in the past several years. Laboratory techniques for diagnosis, although not widely available, now exist, and an effective form of therapy has been developed. Lest we become overconfident in our newly found knowledge, it should be noted that the epidemiology, pathogenesis and means of prevention of *C difficile* toxin-induced diarrhea remain obscure. The mechanism of action of the toxin has not been determined nor has a simple and rapid diagnostic test been developed. Moreover, the cause of toxin-negative antimicrobial-associated diarrhea remains unknown.

Addendum

Since preparation of this manuscript, several important papers regarding *C difficile* and diarrhea have been published. Members of the cephalosporin group of antimicrobials are undoubtedly a more frequent cause of *C difficile*-induced diarrhea than previously noted; Bartlett and colleagues[85] reported *C difficile*-induced pseudomembranous colitis in 17 patients who had been treated with a cephalosporin.

In regard to therapy of *C difficile*-induced diarrhea, orally given vancomycin was found to be effective therapy in a series of 79 patients.[86] Symptomatic relapse after discontinuation of vancomycin, however, occurred in 14 percent of cases treated; this finding underscores the need for careful follow-up of patients treated for colitis with vancomycin. Chang and co-workers[87] have shown resolution of *C difficile*-induced diarrhea in four patients treated with bacitracin given orally (relapse occurred in one of the four subjects, however). A review of therapy and prevention of *C difficile*-induced diarrhea has recently been published and guidelines for therapy formulated.[88] Mulligan and colleagues[89] have recently documented extensive hospital environmental contamination by *C difficile* in the vicinity of several patients with antimicrobial-associated diarrhea; although the significance of this contamination is not clear, it might be a mechanism by which nosocomial spread of infection could occur.

Finally, preliminary data regarding a second toxin ("enterotoxin") of *C difficile* have been published.[90] Although this "new" toxin may eventually be shown to be important in the pathogenesis of disease, the cytotoxin (as indicated above) remains the best marker at this time for *C difficile*-induced diarrhea.

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